

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
29 March 2001 (29.03.2001)

PCT

(10) International Publication Number
WO 01/21656 A3(51) International Patent Classification⁷: **C07K 14/32**,
19/00, 14/25, A61K 39/07, 48/00, 39/108

(21) International Application Number: PCT/US00/26192

(22) International Filing Date:
22 September 2000 (22.09.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/155,961 24 September 1999 (24.09.1999) US(71) Applicant (for all designated States except US): **THE GOVERNMENT OF THE UNITED STATE OF AMERICA**, as represented by **THE SECRETARY, DEPARTMENT OF HEALTH AND HUMAN SERVICES** [US/US]; Office of Technology Transfer, 6011 Executive Boulevard, Suite 325, Rockville, MD 20852-3804 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **LEPPLA, Stephen, H.** [US/US]; 9501 Starmont Road, Bethesda, MD 20817 (US). **LIU, Shi-Hui** [CN/US]; 1001 Rockville Pike #1822, Rockville, MD 20852 (US). **NETZEL-ARNETT, Sarah**[US/US]; 17100 Dowing Street, #201, Gaithersburg, MD 20877 (US). **HANSEN-BIRKEDAL, Henning** [DK/US]; 2 West Drive, Bethesda, MD 20814 (US). **BUGGE, Thomas** [DK/US]; 9802 Bristo Square Lane, #302, Bethesda, MD 20814 (US).(74) Agents: **PARENT, Annette, S.** et al.; Townsend and Townsend and Crew LLP, 8th floor, Two Embarcadero Center, San Francisco, CA 94111-3834 (US).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

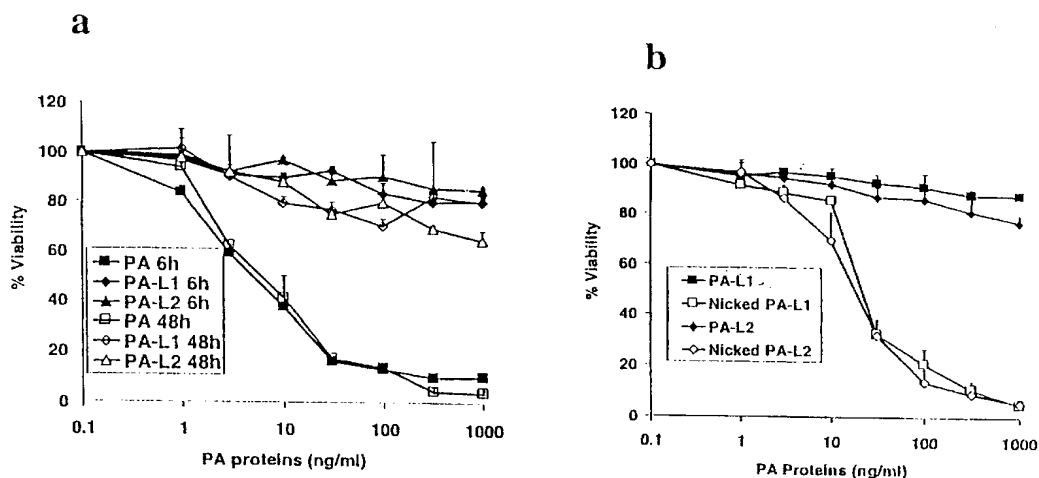
(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

[Continued on next page]

(54) Title: MUTATED ANTHRAX TOXIN PROTECTIVE ANTIGEN PROTEINS THAT SPECIFICALLY TARGET CELLS CONTAINING HIGH AMOUNTS OF CELL-SURFACE METALLOPROTEINASES OR PLASMINOGEN ACTIVATOR RECEPTORS



(57) Abstract: The present invention provides methods of specifically targeting compounds to cells overexpressing matrix metalloproteinases, plasminogen activators, or plasminogen activator receptors, by administering a compound and a mutant protective antigen protein comprising a matrix metalloproteinase or a plasminogen activator-recognized cleavage site in place of the native protective antigen furin-recognized cleavage site, wherein the mutant protective antigen is cleaved by a matrix metalloproteinase or a plasminogen activator overexpressed by the cell, thereby translocating into the cell a compound comprising a lethal factor polypeptide comprising a protective antigen binding site.



(88) Date of publication of the international search report:
17 January 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/26192

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07K14/32 C07K19/00 C07K14/25 A61K39/07 A61K48/00
A61K39/108

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, MEDLINE, BIOSIS, EMBL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 677 274 A (NICHOLS PETER J ET AL) 14 October 1997 (1997-10-14) column 1, line 9 - line 17 column 3, line 27 - line 31 column 4, line 12 - line 19 column 10, line 5 -column 11, line 60 ---	1-24
A	US 5 817 771 A (BAYLEY HAGEN ET AL) 6 October 1998 (1998-10-06) figure 10 column 8, line 7 - line 40 example 3 --- -/--	1-24

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

* & * document member of the same patent family

Date of the actual completion of the international search

18 June 2001

Date of mailing of the international search report

25/06/2001

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

van Klompenburg, W

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/26192

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>LIAW L ET AL: "FUNCTIONS OF THE EXTRACELLULAR MATRIX AND MATRIX DEGRADING PROTEASES DURING TUMOR PROGRESSION" BRAZILIAN JOURNAL OF MEDICAL AND BIOLOGICAL RESEARCH,BR,RIBEIRAO PRETO, vol. 32, no. 7, July 1999 (1999-07), pages 805-812, XP000872134 ISSN: 0100-879X page 809 -page 810</p> <p>-----</p>	<p>1-3,6-9, 23,24</p>
A	<p>MAZAR ET AL: "High-affinity, small cyclic peptide urokinase plasminogen activator receptor (uPAR)-targeting ligands localize reporter and therapeutic conjugates to the surfaces of tumor cells and stimulated endothelial cells" PROCEEDINGS OF THE ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH,US,PHILADELPHIA, PA: AACR, vol. 40, March 1999 (1999-03), page 22 XP002131000 abstract</p> <p>-----</p>	<p>1,4,5, 23,24</p>

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int l Application No

PCT/US 00/26192

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5677274 A	14-10-1997	US 5591631 A	07-01-1997
		AT 169959 T	15-09-1998
		AU 682500 B	09-10-1997
		AU 6392294 A	29-08-1994
		CA 2155514 A	18-08-1994
		DE 69412593 D	24-09-1998
		DE 69412593 T	18-02-1999
		EP 0684997 A	06-12-1995
		ES 2122257 T	16-12-1998
		WO 9418332 A	18-08-1994
<hr/>			
US 5817771 A	06-10-1998	AU 4457296 A	24-07-1996
		WO 9620688 A	11-07-1996
		US 5777078 A	07-07-1998
		US 5824776 A	20-10-1998
		CA 2160909 A	10-11-1994
		EP 0753071 A	15-01-1997
		JP 9500102 T	07-01-1997
		WO 9425616 A	10-11-1994
<hr/>			